



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

MEMORANDUM

Date: February 28, 2017

SUBJECT: **Isothiazolone:** Summary of Hazard and Science Policy Council (HASPOC)
Meeting of September 1, 2016: Recommendations on the Need for Acute and
Subchronic Neurotoxicity Studies Waiver Requests.

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107104, 098901, 098951, and
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5, 4299-07-4, and 2527-66-4

MRID No.: N/A

40 CFR: N/A

FROM: Sarah Dobreniecki, Ph.D., Executive Secretary
HASPOC
Health Effects Division (7509P)

THROUGH: Jeff Dawson, Co-Chair
Anwar Dunbar, Ph.D., Co-Chair
HASPOC
Health Effects Division (7509P)

TO: Jonathan Chen, Ph.D., Toxicologist
Steven Weiss, Branch Chief
RASSB, Antimicrobials Division (7510P)

MEETING ATTENDEES:

HASPOC Members: Anna Lowit, Elizabeth Mendez, John Kough, Jonathan Leshin, Michael
Metzger, Ray Kent

Presenter: Jonathan Chen

Other Attendees: Hannah Pope-Varsalona, Joey Beaver

I. PURPOSE OF MEETING

The isothiazolone biocides are a class of chemicals commonly used as material preservatives in antimicrobial pesticide products. There are six registered isothiazolone biocides and one new isothiazolone biocide currently undergoing evaluation for registration. These chemicals are presented below.

- 1) 5-Chloro-2-methyl-4-isothiazolin-3-one (CMIT)/ 2-methyl-4-isothiazolin-3-one (MIT) mixed in a 3:1 ratio
- 2) 2-methyl-4-isothiazolin-3-one (MIT) as a single active ingredient
- 3) 4,5-Dichloro-2-n-octyl-4-isothiazolin-2-one (DCOIT)
- 4) 2-n-Octyl-4-isothiazolin-3-one (OIT)
- 5) 1,2-Benzisothiazolin-3-one (BIT)
- 6) 1,2-Benzisothiazolin-3-one, 2-butyl (BBIT)
- 7) 1,2-Benzisothiazolin 3-one,2-methyl (Methyl-BIT or mBIT); not currently registered.

Based on the current 40 CFR Part 158W Toxicology Data Requirements, neurotoxicity studies (acute and subchronic) are required for each of the isothiazolone chemicals. There is no neurotoxicity study submitted in any of these isothiazolone biocides. The Hazard and Science Policy Council (HASPOC) met on September 1, 2016 to discuss the need for acute neurotoxicity study (ACN) and/or subchronic neurotoxicity study (SCN) for all these isothiazolone biocides.

II. SUMMARY OF USE PROFILE, EXPOSURE, AND HAZARD CONSIDERATIONS

a. Use and Exposure Profile

The isothiazolone biocides are a class of chemicals commonly used as material preservatives in antimicrobial pesticide products for the control of bacteria, fungi, and/or algae. These pesticide products can be used in/on countertops/utensils (food use), pulp and paper (food packaging), vinyl flooring, household cleaning products, laundry detergent, metalworking fluids, paint (in-can preservative, including paint for ship hulls), plastics, textiles/carpets and wood (pressure treatment).

b. Toxicity Use Profile

The available information for all the isothiazolone chemicals was presented to the Toxicology Science Advisory Council (ToxSAC), at the May 21, 2015 meeting, and TOXSAC concluded that it is appropriate to bridge the chemicals into one group based on the similarity of the toxicology profiles. All effects through all routes of exposure (oral, dermal and inhalation) are point of contact irritation-like effects. The primary effects through the oral route of exposure are irritation-like effects in the upper GI tract, including stomach lesions, irritation, hyperplasia/hyperkeratosis of the squamous epithelium of the forestomach, etc. Through the dermal route of exposure, skin irritation including hyperkeratosis, acanthosis, hyperplasia and inflammation, etc. were seen as the primary concern. In the available inhalation studies, the primary effects are histopathological alterations observed in the nose, larynx, and lungs. ToxSAC concluded that for

risk assessment purposes, chemical-specific data should be used when available. When chemical-specific data are not available, the most conservative endpoint for which there is data from other isothiazolones should be used.

III. STUDY WAIVER REQUESTS

Acute neurotoxicity (ACN) and subchronic neurotoxicity (SCN) studies are required in the 2007 revised 40 CFR Part 158 Toxicology Data Requirements because they provide important scientific information on potential nervous system effects from pesticide exposure. These studies can provide data on a wide range of functional tests for evaluating neurotoxicity including effects on sensorimotor, neuromuscular, activity, and autonomic functions, and histopathology of the nervous system.

1. **Evidence for neurotoxicity in the isothiazolone database:** There are no signs of neurotoxicity in the available acute or repeat dose toxicity studies database for isothiazolone. The toxicity profile for isothiazolone indicates that irritation-like effects are the primary concern through all different routes of exposure (oral, dermal and inhalation).
2. **Risk Assessment Considerations:** Irritation-like effects were the most sensitive effect observed and an ACN or SCN study would likely not identify a lower point of departure (POD) or more sensitive endpoint for risk assessment.

The HASPOC recommends, based on a WOE approach, that the neurotoxicity studies (ACN and SCN) be waived for the isothiazolones. This approach considered all of the available hazard and exposure information for isothiazolone including: (1) a lack of evidence of neurotoxicity in the toxicity database for the isothiazolones; (2) neurotoxicity studies are not likely to identify a lower POD or a more sensitive endpoint for the risk assessment; and (3) the use pattern of the isothiazolones.

IV. HASPOC CONCLUSIONS

Based on a WOE approach, considering all the available hazard and exposure data for isothiazolone, the HASPOC concludes that the neurotoxicity studies (ACN and SCN) for isothiazolone **are not required** at this time.